REMARKS

Telephone Interview

Applicants express appreciation to Examiner Anand Desai and Examiner Robert Wax for the courtesy extended to Applicants' representative, Angela Sebor (undersigned) and inventor Dr. Gary Brodsky during the telephone interview conducted on April 10, 2007.

During the interview, the rejections of Claims 1-8, 14, 46, 58, 59 and 60 under 35 U.S.C. §102 and of Claims 1-8, 14, 46-48, 50-52 and 58-60 under 35 U.S.C. §112, first paragraph (written description and enablement) were discussed. Applicants' representative agreed to amend the phrase "consisting essentially of" to "consisting of" in order to obviate the Examiner's rejection under 35 U.S.C. §112, second paragraph. In addition, with regard to the recitation of 70% identity with respect to SEQ ID NO:2, Applicants' representative referred to the description in the specification of five, different, functional species of the peptide which in most cases are less than 70% identical to one another, and further discussed the demonstration by Dr. Brodsky in the November 3 Declaration that a peptide that is less than 50% identical to SEQ ID NO:2 functions as SEQ ID NO:2. The Examiners encouraged Applicants' representative to reiterate this argument in the current response for reconsideration of these claims. Applicants' agent agreed to limit claims directed to SEQ ID NO:4 to recitation of proteins that are at least 95% identical and have a defined function. In addition, Applicants' agent agreed to recite the functions of prelamin A and lamin A in the claim and to consider separating Claim 14 into two claims, one regarding prelamin A and one regarding lamin A. Amendment of Claim 14 to use the term "conjugated" instead of "attached" was also discussed. Finally, Applicants' agent noted that with regard to the rejections under 35 U.S.C. § 102, the claims in question have an additional element of the conjugated agent which appears not to have been considered by the Examiner, and the Examiners agreed to reconsider these claims.

Claim Amendments

It is noted that Claim 23 and new Claims 61-62 are marked with non-conventional status indicators (*i.e.,* Withdrawn-Amended, or Withdrawn-New). However, this is done for the Examiner's convenience and since the status of the claim is still clear as withdrawn, it is Applicants' understanding that these status indicators should be accepted by the Examiner.

The claims have been amended to clarify the invention.

The amendment to Claim 1, part (d), is supported in the specification on page 20, lines 18-22, and page 36, line 28 to page 37, line 2.

The amendment to Claim 14 includes a clerical amendment to move the "wherein" clause from the end of the claim to the beginning of the claim for clarity. The amendment to use the term "conjugated" with respect to the therapeutic agent, as suggested by the Examiner, is supported in

the specification on page 21, lines 10-11. The amendment to recite that the prelamin A protein of SEQ ID NO:4 "promotes myoblast differentiation" is supported on page 24, lines 19-28.

The amendment to add the sequence identifiers to Claim 23 is found in the specification on page 19, lines 9-22.

The amendments to Claims 46, 47, 48, and 58 are supported by the prior amendment to Claim 1, and is further supported on page 18, lines 5-10 and on page 21, lines 12-14.

New Claims 61 and 62 are supported on page 18, lines 5-10, page 21, lines 12-14 and page 54, lines 17-26 and page 56, lines 1-4.

All other amendments are believed to be clerical in nature, since they merely remove recited subject matter or reorganize recited subject matter for clarity.

Rejection of Claims 1-8, 14, 46 and 58 Under 35 U.S.C. § 112, Second Paragraph:

The Examiner has rejected Claims 1-8, 14, 46 and 58 under 35 U.S.C. § 112, second paragraph, contending that these claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner contends that the claims are drawn to a peptide "consisting essentially of" an amino acid sequence and asserts that, despite the definition in the specification, it is still unclear if the phrase would encompass other embodiments. In later rejections in this Office Action, the Examiner continues to construe the phrase as meaning "comprising".

Without acquiescing to the rejection, and in order to expedite prosecution, the claims have been amended to replace the phrase "consisting essentially of" with the phrase "consisting of". Accordingly, it is believed that this rejection is moot and the Examiner is respectfully requested to withdraw the rejection of Claims 1-8, 14, 46 and 58 under 35 U.S.C. § 112, second paragraph.

Objection to the Specification and Rejection of Claims 1-8, 14, 46-48, 50-52 and 58-60 Under 35 U.S.C. § 112, First Paragraph (Enablement):

The Examiner has objected to the specification and rejected Claims 1-8, 14, 46 and 58 under 35 U.S.C. § 112, first paragraph, on the basis of enablement. Specifically, the Examiner contends that the specification is enabling for a composition comprising prelamin A (SEQ ID NO:4) or the prelamin A peptide with a single modification that affects formation of nuclear lamina structures and the differentiation of cardiac and skeletal myoblast, but does not enable fragments, peptides that differ by at least one substitution, deletion, or insertion, or peptides that are at least 70% identical to SEQ ID NO:2 or SEQ ID NO:4. The Examiner reasons that the pages of the specification cited by the Applicants in the last response make assumptions about the function of SEQ ID NO:2 based on analogy to a yeast protein. With regard to the Declaration under 37 CFR 1.132 of Dr. Brodsky, the Examiner contends that because the last sentence in paragraph 4 states that peptide-treated H9c2 cells show modest increases in lamin A/C and prelamin A expression, it is not clear from the data that myoblast differentiation would not

proceed due to the increased expression of the prelamin A pool. The Examiner contends that the assay presented does not differentiate the effects of prelamin A or lamin A from the prepeptide of prelamin A, and asserts that the myoblast differentiation could be due to the increased expression of processed prelamin A without the prepeptide segment.

Initially, it is noted that fragments of SEQ ID NO:2 are no longer claimed, and that the fragment of SEQ ID NO:4 consists of the majority of the protein, combined with the recitation of a clear biological activity of prelamin A, as discussed in the April 10 interview. Applicants have not presented a separate claim to lamin A, but instead have removed this reference and recited the more specific function for prelamin A activity of promoting myoblast differentiation for prelamin A, since prelamin A promotes and mediates multiple steps involved in myoblast differentiation.

With regard to the function of SEQ ID NO:2, the Examiner contends that the specification does not make and use any modified prelamin A prepeptide in an assay to identify a function for SEQ ID NO:2. In response, Applicants initially reiterate that the specification clearly teaches that the prelamin A prepeptide is a signaling molecule that promotes myoblast differentiation. On page 12, lines 5-9, the specification teaches that the prelamin A prepeptide sequence functions as a signaling molecule when proteolytically released from the prelamin A protein, indicating the proximity and direction of mononucleate myoblasts during differentiation and cell fusion to generate multinucleate myocytes. On page 13, lines 21-24, the specification teaches that the prelamin A prepeptide functions in the intercellular signaling between mononucleated myoblasts during cell fusion and the formation of multinucleated myocytes. On page 18, lines 6-14, the specification teaches that prelamin A prepeptide can be used for the promotion of myoblast activation and differentiation. On page 21, lines 12-20, the specification teaches that the prelamin A prepeptide promotes cell fusion and regeneration of cardiac and skeletal myocytes, and promotes myocyte differentiation and myocyte organization. These teachings are based on the data provided in the Examples, where the inventor showed that defects or deficiencies in the processing of prelamin A results in severely aberrant cardiac and skeletal myocyte differentiation, leading the inventor to conclude that the prelamin A prepeptide functions as a signaling molecule for differentiation of myoblasts. The specification provides a detailed description of the peptides encompassed by the full scope of the claims, including a *detailed* discussion of where the peptides can be modified and retain function (pages 35-37). The differentiation assays in the Examples using C2C12 cells teach one of skill in the art how to test for differentiation of myoblasts. Accordingly, the specification teachings as filed fully enable one of skill in the art to make and use the invention.

The Examiner appears to doubt that the prelamin A prepeptide will work as claimed, without providing evidence or reasoning that is inconsistent with this teaching by the specification. However, the courts have held that whenever a rejection on the basis of enablement is made, "it is incumbent upon the Patent Office....to explain *why* it doubts the truth or accuracy

of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." 439 F.2d at 224, 169 USPQ at 370. Also, an applicant need not have actually reduced every embodiment of the invention to practice prior to filing. "The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." In *Gould v. Quigg* 822 F.2d at 1078, 3 USPQ2d at 1304 (quoting *In re Chilowsky*, 229 F.2d 457, 461, 108 USPQ 321, 325 (CCPA 1956)). Moreover, Applicants have now provided factual evidence supporting the specification teaching that prelamin A prepeptides (meeting the full scope of the claim and beyond) promote myoblast differentiation.

With regard to the Examiner's assertion that the experiments provided in the Declaration under 37 CFR 1.132 of Dr. Brodsky do not differentiate between the effects of prelamin A or lamin A or the prepeptide of prelamin A, Applicants respectfully disagree. As discussed in the April 10 interview and as explained by Dr. Brodsky, the experiments presented in the Declaration were *controlled* experiments that clearly showed that the addition of the *prepeptide* of prelamin A (SEQ ID NO:2 or SEQ ID NO:17) was the cause of induction of myoblast differentiation.

To summarize those experiments, in paragraph 4 of the Declaration, mouse C2C12 skeletal myoblasts or H9c2 rat cardiac myoblasts were exposed to SEQ ID NO:2 (human prelamin A prepeptide). In paragraph 5, mouse C2C12 myoblasts were exposed to SEQ ID NO:17 (chicken prelamin A prepeptide). Control cultures were not exposed to peptide. See also Figs. A-D provided with the Declaration.

In all three experiments, addition of the prelamin A prepeptide induced myoblast fusion, myocyte activation, myocyte differentiation, and myocyte organization in these myoblast cultures. As was emphasized by Dr. Brodsky in the April 10 interview, it is *the addition of the peptide* that causes this activity, since in the absence of the added peptide, the cultures do not differentiate (see also Figs. A-D provided with the Declaration). Accordingly, the Examiner's statement that the "myoblast differentiation could be due to the increased expression of processed prelamin A without the prepeptide segment" can not be correct. Most simply phrased, in the absence of exposure to prepeptide, the cells do not differentiate; after the prepeptide is added, the cells differentiate. Therefore, the prepeptide promotes myoblast differentiation as claimed.

With regard to the Examiner's comment regarding the prelamin A and lamin A pools, as explained by Dr. Brodsky during the April 10 interview, because the prepeptide functions as a *signaling* molecule that initiates a variety of downstream events, it is likely that preformed pools of prelamin A and lamin A will perpetuate the differentiation process (*i.e.,* the prepeptide signals downstream events that result in *additional processing* of preformed prelamin A, which releases *additional prepeptide*, among other downstream events that can be mediated by prelamin A, but

which are induced by the prepeptide signal). However, without the addition of the peptide in these experiments in the first place, the process of differentiation is not initiated.

Moreover, as discussed in the Declaration, in the last filed response and with the Examiners during the April 10 interview, these experiments provide additional supporting evidence that a prelamin A prepeptide that is at least 70% identical to SEQ ID NO:2, that has one substitution, deletion or insertion as compared to SEQ ID NO:2, or that has a substitution at positions 1, 4, 5, 6, 9, 11 and 14 as compared to SEQ ID NO:2, each promote myoblast differentiation. The Examiners asked that this argument be reiterated for consideration of claims to 70% identity in particular, and so the following arguments address this issue.

Indeed, the chicken prelamin A prepeptide that was used in the experiments in paragraph 5 of the Declaration is only about 53% identical to SEQ ID NO:2, yet has the same function as SEQ ID NO:2. The Examiner is respectfully reminded that the chicken prelamin A prepeptide contains a substitution, as compared to SEQ ID NO:2, at each of positions 1, 4, 5, 6, 9, 11 and 14, *as well as* two insertions between residues 12 and 13 with respect to SEQ ID NO:2. Teachings regarding making such substitutions and insertions are in the specification as filed on pages 35-37 and in Figure 2.

The experiment provided in the Declaration demonstrates that *multiple* substitutions and insertions can be made in SEQ ID NO:2, all in accordance with what is taught in the specification on pages 35-37, while retaining the biological activity of the prelamin A prepeptide. Indeed, even a substitution at position 4, which is highly conserved among other animal species (see Fig. 2 of the application), retains the activity of SEQ ID NO:2. The specification also provides three additional species of prelamin A prepeptide (see Fig. 2, for example) that illustrates where in the protein modifications can be tolerated. This teaching is underscored by the demonstration of the activity of both chicken and human prelamin A prepeptide on myoblasts from a different species of animal. Specifically, as discussed previously, both human and chicken prepeptide induces differentiation of *mouse* myoblasts, and the human peptide was also shown to induce differentiation of rat myoblasts.

Since the claimed peptides (having 70% identity to SEQ ID NO:2 or having the modifications recited in Claim 1(c) and (d)) are more similar to SEQ ID NO:2 than the chicken prelamin A prepeptide represented by SEQ ID NO:17 and illustrated in the Declaration, it is asserted that these data clearly support Applicants' contention that one of skill in the art is enabled to make and use the invention as presently claimed.

With regard to SEQ ID NO:4 and Claim 14, as agreed with the Examiners during the April 10 interview, Applicants have amended this claim to recite a clear function for prelamin A as disclosed and demonstrated in the specification. The specification provides sufficient guidance regarding what residues of prelamin A (SEQ ID NO:4) are predicted to tolerate modification, including any of the modifications described above with respect to SEQ ID NO:2, which are

applicable to SEQ ID NO:4. The specification also provides evidence that at least six different mutations in prelamin A are asserting their effect by negatively impacting prelamin A processing, thus providing information regarding residues that should be avoided in order to produce a functional prelamin A. Furthermore, at the time of the invention, the nucleic acid and amino acid sequences of prelamin A were known for a variety of animal species, including, but not limited to: human mouse, chicken, *Xenopus laevis* (African clawed frog), and *Danio rerio* (zebra fish). These are all provided by the present specification and are more divergent than the claimed 95% identity. Combined with the functional recitation, it is submitted that the specification is fully enabling with respect to Claim 14.

In view of the foregoing remarks, the Examiner is respectfully requested to withdraw the rejection of Claims 1-8, 14, 46 and 58 under 35 U.S.C. § 112, first paragraph, enablement.

Objection to the Specification and Rejection of Claims 1-5, 7, 8, 14, 46, 47, 48, 50, 51 and 58-60 Under 35 U.S.C. § 112, First Paragraph (Written Description):

The Examiner has objected to the specification and rejected Claims 1-5, 7, 8, 14, 46, 47, 48, 50, 51 and 58-60 under 35 U.S.C. § 112, first paragraph, on the basis of written description. The Examiner contends that the specification does not use any modified prelamin A prepeptide in assays to identify a function for SEQ ID NO:2. In addition, the Examiner asserts that the Declaration under 37 CFR 1.132 of Dr. Brodsky is not sufficient to overcome the rejection because the experiments in the Declaration allegedly do not differentiate effects of prelamin A or lamin A from the prepeptide of prelamin A. The Examiner contends that the biological activity of SEQ ID NO:2 is not described. With regard to SEQ ID NO:4, the Examiner contends that the specification does not describe the genus of prelamin A peptides that retain prelamin A or lamin A biological activity.

Applicants traverse the rejection of Claims 1-5, 7, 8, 14, 46, 47, 48, 50, 51 and 58-60 under 35 U.S.C. § 112, first paragraph. First, with regard to the Examiner's contention that the specification does not use any modified prelamin A prepeptide in assays to identify a function for SEQ ID NO:2, Applicants submit that the specification provides a myoblast differentiation assay (see Example 2, for example) and further teaches that prelamin A prepeptide can be used for the promotion of myoblast activation and differentiation (page 18, lines 6-14), and that the prelamin A prepeptide promotes cell fusion and regeneration of cardiac and skeletal myocytes, and promotes myocyte differentiation and myocyte organization (page 21, lines 12-20). The Examiner is respectfully reminded that this is an issue of *description*. The specification teaches that the prelamin A prepeptide promotes myoblast differentiation as claimed and provides an assay for assessing this function. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was

complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. *See, e.g., Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998). In the present case, the specification as filed sufficiently describes the invention in a manner that demonstrates the inventor's possession of the invention.

With regard to the Examiner's concerns regarding the Declaration of Dr. Brodsky, since this was discussed in detail above under the enablement rejection, and since the concerns expressed are the same in this rejection, the argument will not be reiterated here.

With regard to the scope of the claimed peptides, the present specification provides significant guidance at page 34, line 17 to page 37, line 2, with respect to which of *each* of the positions of the 15 amino acid sequence of SEQ ID NO:2 are candidates for modification and which are not. The accuracy of this description is *clearly* shown by the evidence provided in the attached Declaration that demonstrates that peptides with far greater variation than that claimed, including at the specific positions identified by the inventor in the original specification, retain biological activity, as clearly predicted and stated by the inventor. The specification clearly discusses the impact of modification *at each position of SEQ ID NO:2* and clearly notes those residues that are important for function (*e.g.,* the cysteine residue at position 15 of SEQ ID NO:2). This is indeed a sufficient description to show possession of the invention and is corroborated by the specification and Declaration under 37 CFR § 1.132. Moreover, Applicants again assert that the number of variants encompassed by the claims is *not* large, noting that at 70% identity, only 4 or fewer amino acids can be modified. Indeed, the peptide described in the experiments in the Declaration is biologically active at only 53% identity to SEQ ID NO:2.

With regard to SEQ ID NO:4 and Claim 14 and dependent claims thereof, the specification has taught which residues are most important to the function of prelamin A by noting residues that are important with respect to the processing site and by identifying residues that, if modified, can render the prelamin A processing-deficient. The specification has provided an extremely detailed discussion of where the portion of SEQ ID NO:4 containing the signaling peptide of SEQ ID NO:2 can be modified, which is clearly demonstrated to be accurate by the supporting data provided with this response. One of skill in the art is readily able to envision proteins that are 95%, 97% or 99% identical to SEQ ID NO:4, and the specification provides assays that can be used to evaluate the function of the proteins.

In view of the foregoing remarks, the Examiner is respectfully requested to withdraw the rejection of Claims 1-5, 7, 8, 14, 46, 47, 48, 50, 51 and 58-60 under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 1-8, 46, 58 and 59 Under 35 U.S.C. § 102(b):

The Examiner has rejected Claims 1-8, 46, 58 and 59 under 35 U.S.C. § 102(b) in view of Kilic et al. Specifically, the Examiner contends that Kilic et al. disclose the synthesis of a peptide that has 100% identity to SEQ ID NO:2, with the insertion of three amino acids at the amino terminus. The Examiner states that the phrase "consisting essentially of" is given the meaning "comprising" for the purpose of applying the rejection.

Applicants traverse the rejection of Claims 1-8, 46, 58 and 59 under 35 U.S.C. § 102(b). While Applicants do not agree that the phrase "consisting essentially of" was properly interpreted given the definition in the specification, to expedite prosecution, the phrase has been replaced with the term "consisting of". Kilic et al. do not teach or suggest a peptide consisting of SEQ ID NO:2 or such a peptide with any of the recited modifications.

In view of the foregoing remarks, the Examiner is respectfully requested to withdraw the rejection of Claims 1-8, 46, 58 and 59 under 35 U.S.C. § 102(b).

Rejection of Claims 14 and 60 Under 35 U.S.C. § 102(e):

The Examiner has rejected Claims 14 and 60 under 35 U.S.C. §102(e), in view of Eriksson et al. The Examiner asserts that Eriksson et al. describe a substantially purified lamin A protein that is 100% identical to SEQ ID NO:4 from amino acid residues 1 to 606.

Applicants traverse the rejection of Claims 14 and 60 under 35 U.S.C. § 102(e). As discussed with the Examiners during the April 10 interview, Claims 14 and 60, in addition to reciting SEQ ID NO:4, also recite the conjugation (previously recited as an attachment) of SEQ ID NO:4 to another agent that increases the half-life of SEQ ID NO:4. Eriksson et al. do not teach or suggest the claimed protein that is conjugated to a therapeutic agent that increases the half-life of the protein and therefore can not anticipate the claims.

In view of the foregoing discussion, the Examiner is respectfully requested to withdraw the rejection of Claims 14 and 60 under 35 U.S.C. §102(e).

Applicants have attempted to respond to all of the issues raised by the Examiner in the January 30, 2007 Office Action. In an effort to expedite prosecution of the claims, the Examiner is encouraged to contact the below named agent to discuss any remaining issues.

Respectfully submitted,

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